REMARKS

Claims 1-58 are cancelled, claims 62 and 66-87 are withdrawn by the Examiner, and claims 59-61 and 63-65 were examined and rejected.

Claims 59 and 66 are amended to further clarify the claimed invention.

Applicants respectfully request reconsideration in view of the remarks set forth below.

No new matter is added.

Specification

The disclosure is objected to for referring to peptide sequence that are not accompanied by an identifier.

The paragraphs starting on lines 7 and 17 of page 60 have been amended to recite a SEQ ID NO.

This objection has been addressed and may be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 59-61 and 63-65 are rejected for failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Applicants respectfully disagree.

With regard to the written description requirement of 35 U.S.C. § 112, the MPEP explicitly states that the description need only describe in detail that which is new or not conventional."[1] Accordingly, if an element of a claim is not new, it does not have to be described in any detail.

What is presently claimed is a retroviral vector encoding a fusion protein, a so called "split intein" protein, that is capable of cyclizing a polypeptide of interest (which is positioned within the fusion protein) to form a cyclic polypeptide. As discussed in the background section of the instant application, and as the Office has correctly pointed out in the rejection under 35 U.S.C. § 103, split intein proteins for the production of cyclic peptides are known in the art.

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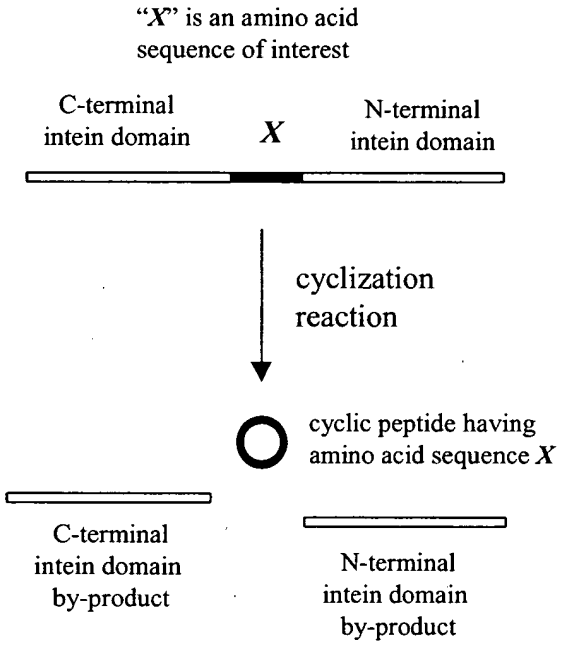
[1] MPEP § 2163 "The description need only describe in detail that which is new or not conventional.", citing *Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94.

In view of the guidance regarding the requirements for written description set forth in the MPEP, and further because split intein proteins are known in the art, the Applicants respectfully submit that the fusion polypeptides recited in the claims do not need to be described in any detail.

A description of a claim-recited fusion polypeptides is found in Fig. 1B, retroviral vectors disclosed on page 24 lines 1-2, and an example of a claim-recited retroviral vector is explicitly set forth in Fig. 15A.

The following figure diagrams what is shown in Fig. 1B, modified to incorporate language used in the claims at issue:



In short, the intein domains of the fusion protein cause cyclization of "X" – the amino acid sequence of interest. The reaction produces three products: the cyclic peptide, and the two intein domain by-products.

In view of the foregoing, the Applicants respectfully submit according to the guidance set forth in the MPEP, the claimed invention, i.e., a retroviral vector encoding a split-intein fusion polypeptide, is adequately described in the instant application.

Further, as would be recognized by one of skill in the art and as explained on page 9, lines 8-25 of the instant specification, any synthetically-made or naturally-occurring "split" (i.e., "*trans*-splicing ") intein can be used in the subject methods. Naturally-occurring split inteins (e.g., the Ssp dnaE intein) and artificially split inteins were well known in the art prior to the priority date of the instant application (see exemplary Exhibits A-F, enclosed herewith and cited in the Information Disclosure Statement submitted herewith). Further, a listing of 22 exemplary inteins suitable for use in the subject methods is found in the last paragraph of page 9 and the second paragraph of page 10. Figures 3-5 show the nucleotide and amino sequences of these inteins. Accordingly, at least 22 inteins suitable for use in the claimed methods are explicitly recited in the specification, and many others would have been apparent to one of skill in the art in view of what was already known at the time of filing. Accordingly, the Applicants respectfully submit that one of skill in the art, in view of the instant specification and what was known about inteins at the time of filing, would have instantly envisioned numerous intein-based fusion proteins encompassed by the instant claims. The claimed invention, is, therefore, adequately described by the instant application.

Finally, the Office also appears to assert that the invention is inadequately described because there may be undefined variables or factors that affect cyclization efficiency. While the Applicants acknowledge that certain factors may effect cyclization efficiency, there is no evidence that the claim recited fusion peptide cannot be used to make a vast number of cyclic polypeptides having different amino acid sequences. Further, polypeptides that may be circularlized using the subject invention are described in the instant specification, as, e.g., polypeptides having a randomized sequence (see Fig. 15A).

In view of the foregoing discussion, this rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 59-61 and 63-65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office asserts that it is not clear if the peptide of interest is different from the cyclic peptide.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 59 has been amended to recite that the fusion polypeptide contains a peptide comprising "an amino acid sequence of interest" – it is this amino acid sequence that is cyclized.

The Applicants respectfully submit that this rejection has been adequately addressed and may be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 59-61 and 63-65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Scott (Proc. Natl. Acad. Sci. 96: 13638-13643) or Evans (J. Biol. Chem. 275:9091-9094) in view of a patent by Nolan (U.S. Pat. No. 6,153,380). The Examiner reasons that Scott's or Evans' bacterial split intein systems for cyclizing peptides, in combination with Nolan's retroviral vector, renders the claimed invention obvious.

Referring to 35 USC § 103(c), MPEP § 706.02(l)(1) states:

> Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. This change to 35 U.S.C. 103(c) applies to all utility, design and plant patent applications filed on or after November 29, 1999, including continuing applications filed under 37 CFR 1.53(b), continued prosecution application filed under 37 CFR 1.53(d), and reissues."

As such the changes to 35 U.S.C. §103 apply to all utility patent applications filed on or after November 29, 1999. Since the instant application was filed on March 6, 2001, which is after November 29, 1999, §103(c) as set out above applies to the instant application. Thus, if the Nolan patent and the

instant application were owned by the same person or subject to an obligation of assignment to the same person, at the time the instant application was made, the Nolan patent is not available as prior art under 35 USC §103.

This is indeed the case. The invention claimed in the instant patent application was subject to an obligation of assignment to Rigel Pharmaceuticals, Inc. ("Rigel"). An assignment executed by the inventor Todd Kinsella was recorded on August 23, 2001 (Reel/Frame 012115/0311) (copy enclosed).

The Nolan patent cited as art was owned by Rigel at the time the claimed invention in that patent was made, as evidenced by an assignment by the inventor Gary Nolan to Rigel, recorded on October 14, 1997 (Reel/Frame 8875/0682) (copy enclosed).

Thus, as stated in §103(c), the subject matter of the cited Nolan patent and the claimed invention were, at the time the invention was made, both owned by Rigel or both under an obligation of assignment to Rigel. As such the Nolan patent shall not preclude patentability under §103.

Therefore, the Nolan patent is not available as prior art against the claimed invention of the present application. The claims thus cannot be rejected by a combination that relies upon the disclosure of Nolan. Neither Scott nor Evans discloses use of a retroviral vector, nor makes any suggestion that split inteins could be employed in such a vector for expression in an animal cell. Scott and Evans, either taken alone or in combination, fail to provide each and every element of the claimed invention.

Furthermore, even if Nolan were available as prior art, the Applicants respectfully submit that this reference, taken with either or both of Scott and Evans, still does not provide a suggestion to combine their teachings or a reasonable expectation to obtain the present invention. Applicants first point out that cyclic peptides may be made in several different ways, and Nolan only explicitly refers to methods in which peptides are cyclized via a disulphide bond between two terminal cysteine residues. This method, which does *not* involve split inteins, is illustrated in Figs. 3A-3C of Nolan's disclosure. At the time of Nolan, split inteins were not appreciated in the art.

Cyclizing methods involving split inteins, such as the ones referred to by Scott and Evans, represent a completely different method to that explicitly described by Nolan. Further, Scott and Evans only disclose use of split inteins in bacterial hosts and, as noted in the Office Action, do not disclose or suggest use of a retroviral vector, even though retroviral vectors were well known in the art at the time.

There is simply no discussion or suggestion that split inteins could be used in a retroviral vector nor any disclosure or discussion as to how one would express such vectors in an animal host cell.

The Applicants respectfully submit that there is simply no motivation to combine a system for peptide cyclization disclosed in Scott and Evans *only in use in bacterial cells* with the general teachings of peptide cyclization in Nolan. Scott and Evans each disclose *bacterial* split intein-based systems, whereas the instant claims, because retroviral vectors can only be used in animal cells, recite an *animal* split intein system.

Furthermore, Scott and Evans only show that a split intein system works in a bacterial host cell. Nolan discloses that peptide cyclization methods *that do not involve split inteins* would be useful in an animal cell. Given the state of the art at the time of filing of the present application, one of skill in the art would have no reasonable expectation that a split intein system that had only been used in *bacterial* cells, could be used in an *animal* system.

Accordingly, even if Nolan was available as prior art, there is no suggestion of the claimed invention in any of the cited references. Further, Nolan could not be combined with either of Scott or Evans with a reasonable expectation of success.

Accordingly this rejection of claims 59-61 and 63-65 under 35 U.S.C. § 103(a) may be withdrawn.

Information Disclosure Statement (IDS)

An IDS is submitted with this response in order to ensure that references provided as Exhibits A-F are officially made of record and considered by the Examiner. The Examiner is requested to indicate such consideration by initialing the SB08/A form and returning a copy of the initialed form with the next action.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RIGL-022.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 23, 2004

By: _____
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F:\DOCUMENT\RIGL (Rigel)\022\response to OA January 26, 2004.doc

Attachments: Copies of assignments (Reel/Frame 012115/0311; and Reel/Frame 8875/0682)
Exhibits A-F
Information Disclosure Statement, citing references in Exhibits A-F
Revocation/Power of Attorney

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MARCH 05, 1998

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BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

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DOC DATE: 10/14/1997

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PATENT NUMBER:

FILING DATE: 01/23/1997
ISSUE DATE:

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RECORDATION DATE: 08/27/2001

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BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

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